EDITORIAL

The Cardiac Troponin Renal Disease Diagnostic Conundrum

Past, Present, and Future

Articles, see p 425 and p 436

Christopher deFilippi, MD
Stephen Seliger, MD, MS

Nearly 25 years ago, novel assays of cardiac troponin (cTn) emerged as diagnostic and prognostic blood-based biomarkers superior to creatinine kinase isoforms, utilizing the accuracy of immune-assay technology and unique cardiac myocyte-specific epitopes. A new consensus definition of acute myocardial infarction (AMI) ultimately emerged, recommending cTn as the biomarker of choice.[1] This definition reflected an increased emphasis on a biochemical basis for the diagnosis of AMI, particularly for non-ST–elevation AMI (NSTEMI). Two subsequent redefinitions of AMI have further emphasized and refined the role of cTn levels for diagnosis. Most recently, the European Society of Cardiology guidelines, utilizing an extended experience with high-sensitive (hs) cTn assays, have proposed algorithms to triage patients suspected of NSTEMI based on initial, or initial and 1-hour follow-up hs-cTn levels.[2] Both groups presenting their work in this issue of *Circulation* have previously contributed[3,4] to demonstrating the efficacy of such an approach. However, as all clinicians know, the interpretation of cTn levels for the diagnosis of NSTEMI often requires considerable clinical acumen to account for confounding comorbidities. These challenges have led to some trepidation surrounding the introduction of hs-cTn assays into clinical practice in the United States. No comorbidity has resulted in more confusion regarding cTn result interpretation than chronic kidney disease (CKD).[5]

Soon after the first studies demonstrating a poor prognosis in unstable angina patients with elevated cardiac troponin T (cTnT) quantified by first-generation assays, investigators observed that cTnT levels could be chronically elevated in patients with CKD without signs or symptoms of AMI.[6] These findings were initially attributed to a lack of cardiac isoform specificity; however, subsequent versions of the cTn assays confirmed specificity for the cardiac cTn isoform, and additional studies refuted the possibility that patients on dialysis produced cTn from uremic skeletal muscle.[7] By the early 2000s, there was recognition that elevations in cTnT and cardiac troponin I (cTnI) in asymptomatic individuals with CKD were associated with underlying chronic cardiovascular pathology and predicted increased all-cause and cardiovascular mortality.[8] It is also important to note that although many prior reports through the early 2000s asserted that cTnI was less influenced by renal function compared with cTnT, the overall current consensus is that the 2 biomarkers provide similar diagnostic and prognostic information in all patients, with any reported differences in accuracy more influenced by the choice of diagnostic cutoff than by the biological characteristics of the 2 molecules. This finding is borne out by the publications by Miller-Hodges et al[9] and Twerenbold[10] using the hs-cTn assays presented in this issue of *Circulation*.

Initial reports of the diagnostic accuracy for AMI (particularly NSTEMI) with cTn assays in patients with renal disease and signs and symptoms suggestive of AMI

Correspondence to: Christopher deFilippi, MD, Inova Heart and Vascular Institute, Suite I-1225, 3300 Gallows Rd, Falls Church, VA 22042. E-mail Christopher.Defilippi@Inova.org

Key Words: Editorials ■ chest pain ■ myocardial infarction ■ renal insufficiency ■ troponin

showed large heterogeneity. In a 2014 report from the Agency for Healthcare Research and Quality, the sensitivity for cTnT ranged from 71% to 100% and specificity 31% to 86%. For cTnI the results were similar, with a sensitivity ranging from 43% to 94% and a specificity of 48% to 100%.[5] Based on the methodological heterogeneity of these studies with respect to patient populations, diagnostic cutoffs, and adjudication methods for AMI, it is difficult to draw conclusions. Nevertheless, the Agency for Healthcare Research and Quality report concluded that there is, "low-quality or insufficient evidence for the utility of troponin T and troponin I assays for diagnosis and management of ACS [acute coronary syndrome]…in patients with CKD."[5] A major improvement to this limited evidence base was a subsequent publication from the APACE (Advantageous Predictors of Acute Coronary Syndrome Evaluation) investigators in *Circulation* in 2015 evaluating the diagnostic accuracy of an initial value of 3 sensitive cTn and 4 hs-cTn assays in ≈2800 subjects, 447 of whom had an estimated glomerular filtration rate <60 mL/min/1.72 m^2. The investigators found that the overall accuracy in those with impaired renal function was statistically lower than those with preserved renal function, but that these differences were of modest clinical importance. They further suggested that adjustment of the cutoff value of the cTn level to 1 optimized for patients with CKD could improve specificity without an unacceptable loss of sensitivity for NSTEMI.[11] Although it was initially reassuring that cTn and hs-cTn assays had acceptable diagnostic accuracy in patients with CKD not on dialysis, several important issues remained. For example, the accuracy of newer triage approaches (immediate or early triage to 1 of 3 groups: rule-out, observe, or rule-in) remained uncertain for patients with CKD, as did the interpretation of serial changes using an accelerated diagnostic algorithm such as proposed in the European Society of Cardiology guidelines.[2]

The companion publications by Miller-Hodges et al[9] and Twerenbold[10] add substantial insight into the early triage of patients with CKD with suspected NSTEMI and their associated prognosis compared with patients with preserved renal function. First, both studies identify that initially low levels of hs-cTnT and hs-cTnI, utilizing cutoffs derived predominantly among patients with normal renal function, can identify patients with CKD who also have an extremely low probability of NSTEMI and good short-term cardiovascular prognosis. Unfortunately (and unsurprising to clinicians involved in the management and triage of a heterogeneous group of patients presenting with possible AMI), the proportion of patients with CKD who fit into this category is quite small. For Miller-Hodges et al,[9] 17% of those with CKD versus 56% without CKD had an initial hs-cTnI <5 ng/L. For Twerenbold[10] using the same hs-cTnI assay at 0 and 1 hours, proportions were similar for a rapid rule-out: 17% versus 58% for those with versus without CKD. Similar differentiation was seen when hs-cTnT was used. Second, acknowledging the challenges of diagnosing NSTEMI in patients with CKD, the incidence is at least twice as high in those with CKD (30% and 31%, respectively) than those without CKD (15% and 13%, respectively) in the 2 studies. Third, irrespective of whether hs-cTnI or hs-cTnT is measured and whether triage is based on a single initial measure or a 0- and 1-hour measure, a large minority of patients with CKD are going to be characterized as warranting further observation. Based on intermediate hs-cTnI levels, this proportion was 43% and 47%, respectively, in those with CKD versus 29% and 24%, respectively, in those patients without CKD. Similar findings were seen for triage based on hs-cTnT. Only a small minority of patients with CKD in this intermediate range of cTn will ultimately have an adjudicated diagnosis of NSTEMI. Changing diagnostic cut points did not substantially improve the allocation of patients with CKD out of the observation group. Fourth, despite the diagnostic challenges for NSTEMI that remain in this large subgroup of patients with CKD whose cTn levels place them in the observational group, their prognosis remains significantly worse long-term with respect to major adverse cardiac events compared with those patients without CKD in the same group. For example, in the Twerenbold[10] study, when using hs-cTnT to define the observation group, 2-year major adverse cardiac event-free survival is only 79.3% in those with CKD versus 92.5% for those with normal renal function. Similar findings are observed using hs-cTnI. Much of this low-level elevation of hs-cTn likely precedes the emergency department presentation and can be associated with myocardial rather than epicardial coronary pathology. Nevertheless, patients with CKD presenting with symptoms of AMI remain a diagnostic challenge to clinicians relying on cTn assays as the cornerstone for the diagnosis of NSTEMI.

In light of the challenges of accurate rapid triage for NSTEMI in patients with CKD, now extended to the use of hs-cTn assays, what further investigations can help improve the specificity of hs-cTn testing in this large subpopulation of patients presenting for emergency evaluation? Among the many challenges to future investigation is the persistent uncertainty regarding the pathophysiology of chronic low-level elevations of cTn in patients with CKD, with prior studies disagreeing on whether decreased renal clearance or increased cardiac production is primary responsible.[12] Although intact cTnT and cTnI are too large to undergo substantial glomerular filtration, immunoreactive cTn may also circulate in fragments that could plausibly be subject to filtration. A recent study using gel filtration chromatography demonstrated that nearly all circulating cTnT in stable patients with end-stage renal disease represented small (<18 kDa) fragments that were im-

munoreactive using a clinical hs-cTnT assay.[13] This pattern was in contrast to that seen in patients with AMI, in which both intact and primary and secondary fragments of cTnT were present, with only the intact cTnT and larger primary fragments demonstrating assay immunoreactivity. Whether similar patterns of fragmentation are observed in patients with moderate CKD is unknown. However, these findings and those of prior studies raise the possibility that distinct patterns of circulating cTn species may distinguish acute myocardial necrosis from chronic low-level cTn elevations, such as observed in asymptomatic patients with CKD. If these differential patterns are confirmed, then potentially novel assays targeting unique epitopes could be developed to more accurately distinguish acute necrosis from other conditions, such as CKD associated with moderately elevated cTn.

DISCLOSURES

Dr deFilippi receives research support from Roche Diagnostics; receives consulting fees from Alere, FujiRebio, Metanomics, Ortho Diagnostics, Roche Diagnostics, Radiometer, and Siemens Healthcare; is on end point committees for Radiometer and Quintiles; and receives royalties from UpToDate. Dr. Seliger receives research support from Roche Diagnostics.

AFFILIATIONS

Inova Heart and Vascular Institute, Falls Church, VA (C.d.F). Department of Medicine, Division of Nephrology, University of Maryland School of Medicine, Baltimore (S.S.).

FOOTNOTES

Circulation is available at http://circ.ahajournals.org.

REFERENCES

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315. doi: 10.1093/eurheartj/ehv320.
3. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, Strachan FE, Ferry A, Stirzaker AG, Reid A, Gray AJ, Collinson PO, McAllister DA, Apple FS, Newby DE, Mills NL; High-STEACS investigators. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet*. 2015;386:2481–2488. doi: 10.1016/S0140-6736(15)00391-8.
4. Mueller C, Giannitsis E, Christ M, Ordóñez-Llanos J, deFilippi C, McCord J, Body R, Panteghini M, Jernberg T, Plebani M, Verschuren F, French J, Christenson R, Weiser S, Bendig G, Dilba P, Lindahl B; TRAPID-AMI Investigators. Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med*. 2016;68:76.e4–87.e4. doi: 10.1016/j.annemergmed.2015.11.013.
5. Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, Michos ED. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. *Ann Intern Med*. 2014;161:502–512.
6. Li D, Keffer J, Corry K, Vazquez M, Jialal I. Nonspecific elevation of troponin T levels in patients with chronic renal failure. *Clin Biochem*. 1995;28:474–477.
7. Haller C, Zehelein J, Remppis A, Müller-Bardorff M, Katus HA. Cardiac troponin T in patients with end-stage renal disease: absence of expression in truncal skeletal muscle. *Clin Chem*. 1998;44:930–938.
8. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: a meta-analysis. *Circulation*. 2005;112:3088–3096. doi: 10.1161/CIRCULATIONAHA.105.560128.
9. Miller-Hodges E, Anand A, Shah ASV, Chapman AR, Gallacher P, Ken Lee K, Farrah T, Halbesma N, Blackmur JP, Newby DE, Mills NL, Dhaun N. High-sensitivity cardiac troponin and the risk stratification of patients with renal impairment presenting with suspected acute coronary syndrome. *Circulation*. 2018;137:425–435. doi: 10.1161/CIRCULATIONAHA.117.030320.
10. Twerenbold R, Badertscher P, Boeddinghaus J, Nestelberger T, Wildi K, Puelacher C, Sabti Z, Rubini Gimenez M, Tschirky S, du Fay de Lavallaz J, Kozhuharov N, Sazgary L, Mueller D; Breidthardt T, Strebel I, Flores Widmer D, Shrestha S, Miró O, Martín-Sánchez FJ, Morawiec B, Parenica J, Geigy N, Keller DI, Rentsch K, von Eckardstein A, Osswald S, Reichlin T, Mueller C. 0/1-Hour triage algorithm for myocardial infarction in patients with renal dysfunction. *Circulation*. 2018;137:436–451. doi: 10.1161/CIRCULATIONAHA.117.028901.
11. Twerenbold R, Wildi K, Jaeger C, Gimenez MR, Reiter M, Reichlin T, Walukiewicz A, Gugala M, Krivoshei L, Marti N, Moreno Weidmann Z, Hillinger P, Puelacher C, Rentsch K, Honegger U, Schumacher C, Zurbriggen F, Freese M, Stelzig C, Campodarve I, Bassetti S, Osswald S, Mueller C. Optimal cutoff levels of more sensitive cardiac troponin assays for the early diagnosis of myocardial infarction in patients with renal dysfunction. *Circulation*. 2015;131:2041–2050. doi: 10.1161/CIRCULATIONAHA.114.014245.
12. Parikh RH, Seliger SL, deFilippi CR. Use and interpretation of high sensitivity cardiac troponins in patients with chronic kidney disease with and without acute myocardial infarction. *Clin Biochem*. 2015;48:247–253. doi: 10.1016/j.clinbiochem.2015.01.004.
13. Mingels AM, Cardinaels EP, Broers NJ, van Sleeuwen A, Streng AS, van Dieijen-Visser MP, Kooman JP, Bekers O. Cardiac troponin T: smaller molecules in patients with end-stage renal disease than after onset of acute myocardial infarction. *Clin Chem*. 2017;63:683–690. doi: 10.1373/clinchem.2016.261644.